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## MINISYMPOSIUM

# Multimodality evaluation of the pediatric brain: DTI and its competitors

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**Abstract** The development of the human brain, from the fetal period until childhood, happens in a series of intertwined neurogenetical and histogenetical events that are influenced by environment. Neuronal proliferation and migration, cell aggregation, axonal ingrowth and outgrowth, dendritic arborisation, synaptic pruning and myelinisation contribute to the ‘plasticity of the developing brain’. These events taken together contribute to the establishment of adult-like neuroarchitecture required for normal brain function. With the advances in technology today, mostly due to the development of non-invasive neuroimaging tools, it is possible to analyze these structural events not only in anatomical space but also longitudinally in time. In this review we have highlighted current ‘state of the art’ neuroimaging tools. Development of the new MRI acquisition sequences (DTI, CHARMED and phase imaging) provides valuable insight into the changes of the microstructural environment of the cortex and white matter. Development of MRI imaging tools dedicated for analysis of the acquired images (i) TBSS and ROI fiber tractography, (ii) new tissue segmentation techniques and (iii) morphometric analysis of the cortical mantle (cortical thickness and convolutions) allows the researchers to map the longitudinal changes in the macrostructure of the developing brain that go hand-in-hand with the acquisition of cognitive skills during childhood. Finally, the latest and the newest technologies, like connectom analysis and resting state

fMRI connectivity analysis, today, for the first time provide the opportunity to study the developing brain through the prism of maturation of the systems and networks beyond individual anatomical areas. Combining these methods in the future and modeling the hierarchical organization of the brain might ultimately help to understand the mechanisms underlying complex brain structure function relationships of normal development and of developmental disorders.

**Keywords** Brain development · Neuroimaging biomarkers · Diffusion tensor imaging · Connectivity · Cortical thickness · Cortical folding · Premature birth

## Introduction

In order to understand how the brain grows to master complex cognitive functions is a fascinating task of developmental neuroscience. Every step in brain development contains major micro- and macrostructural changes that lead to functional competence from the fetus to the newborn to the child and into adulthood.

Non-invasive neuroimaging has allowed researchers in recent years to start to assess these important structural changes during brain development. The three major structural characteristics of the developing human brain are dynamic changes in cortical thickness, the cortical folds with the complex surface structure tightly linked to functional specificity and the underlying connectivity that provides the basis for functional networks. These three major characteristics of the human brain have an intertwined time course of development in the later fetal and early neonatal life.

Noninvasive imaging modalities such as conventional magnetic resonance imaging, diffusion tensor imaging and functional imaging have for the first time allowed researchers to describe these macro- and microstructural changes and functional maturation in vivo during human brain development.

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Recent major research efforts have: (1) defined the early cortical folding in the developing brain and hence the time-related changes in cortical surface and folding [1–3]; (2) determined the changes in cortical thickness [4] that vary as a function of development, and recent methodological advances have allowed studying these changes from the fetus to the newborn into childhood [5, 6]; (3) established the cortical connections by diffusion tensor imaging (DTI) in the developing human infant [7–10], and (4) defined the intrinsic functional networks that are present in the early developing brain and are measured by resting state fMRI.

### Cortical thickness

During the prenatal and early postnatal development, the telencephalic wall changes drastically. From 9 PCW (post-conceptual weeks) to the first few postnatal months, it is composed of the transient fetal zones that disappear before late infancy. These transient fetal zones (marginal zone, cortical plate, subplate, intermediate zone, subventricular and ventricular zone) are sites of specific neurogenetic and histogenetic events (cellular proliferation and migration, axonal outgrowth and ingrowth, cell aggregation and differentiation [11]). The intensity and occurrence of these neurogenetic events within the specific transient fetal zones change the underlying architecture of cells and fibers resulting in changes of water content and microstructural characteristics of the tissue [12]. Thus, these transient fetal zones, due to the age specific differences in extracellular and intracellular water content, can be reliably seen in conventional T1-weighted and T2-weighted MRI images [12, 13]. Moreover, DTI that relies on the movement of water molecules within a given voxel is able to reveal underlying cytoarchitecture and myeloarchitecture of the tissue within the developing brain [14]. Thus, measures of anisotropy (direction dependent movement of water molecules restricted by fibers) within the transient fetal zones have become a helpful tool in studying the developing brain [15]. The dramatic developmental changes in the cellular (postmigratory neurons and glial cells), fibers (axonal and dendritic networks) and water content within the cortical plate during early development is indirectly reflected in (1) different and age-specific T1-weighted and T2-weighted MRI signal intensity (Fig. 1) and (2) different and age-specific anisotropy [9, 16, 17]. In summary, as the cortical plate matures, it is at first composed of densely packed postmigratory neurons and can be seen as a hyperintense zone compared to subcortical areas on conventional T1-weighted images and a zone with relatively high values of fractional anisotropy due to its radial organisation. After the 24th PCW, the predominance of the subplate zone (transient fetal zone that is placed below the cortical plate and serves as a fiber “waiting compartment”) can be reliably identified on the T1-weighted, fractional anisotropy (FA) and T2-

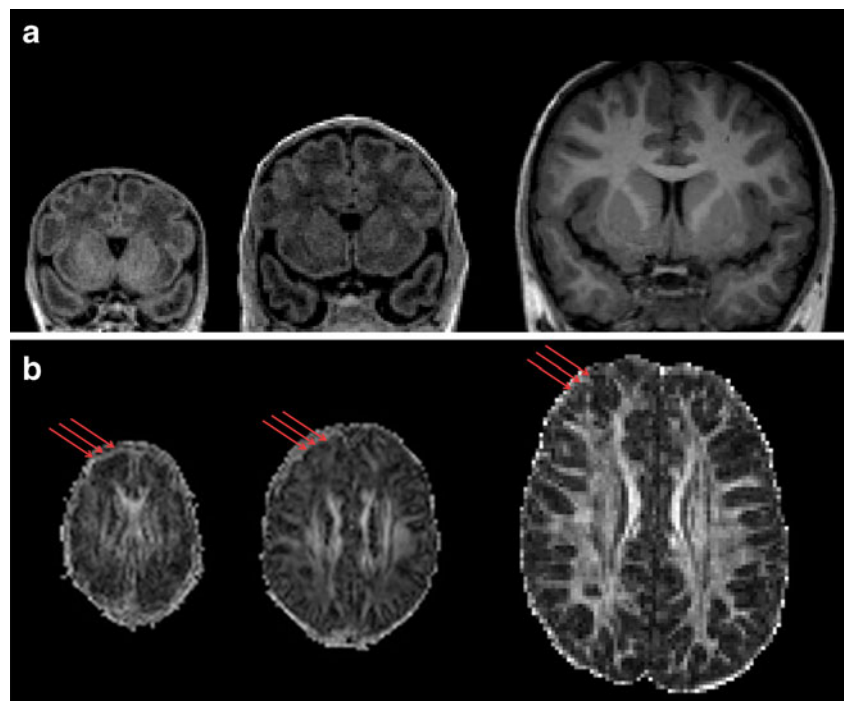
weighted MRI images [12, 15, 18]. At this point of development, the subplate zone is abundant with water, awaiting axonal fibers and extracellular matrix (seen as hypointense zone on T1-weighted MRI images and a zone with low FA values). The ingrowth of axons from the subplate zone into the cortical plate [19], the gradual disappearance of the subplate zone at the late prenatal and early postnatal period, and the consequential growth and arborisation of neuronal dendrites that extend into childhood cause a change into now isotropic movement of water molecules within the cortical plate (cortex after birth). Further, from 1 year up to childhood, the future cortex is identified as a hypointense zone in comparison to the underlying myelinating white matter in T1-weighted MRI images and is characterized by low, isotropic, FA values (Fig. 1).

From this basic image contrast, image analysis-based tools for whole-brain quantitative assessment have been developed to measure cortical volume and thickness measurements [20]. The reliable age-specific processing tools for MRI segmentation of brain tissue during the late prenatal, postnatal and early childhood are challenging [21–26], but major progress has been made with fully automated rater independent segmentation tools even for the newborn brain [23]. Cortical thickness (measured as the shortest length between two adjacent vertex on the cortical and white surface mesh) is dependent on a reliable extraction of gray matter and white matter surfaces. The majority of the techniques designed for the quantitative measurement of the cortex (cortical surface area and thickness) are developed for the analysis of the cortex from mid childhood (6 years) towards the aging population [27, 28]. The neurobiological basis of cortical area and thickness changes [29, 30] computed from MRI images and its genetic background [31] remain an active area of research as well as the correlation with cognitive functions [32]. New techniques of analysis such as the mapping of regions with similar cortical thickness changes throughout development [33], open a new window for mathematical modeling and explanation of cortical growth.

### Cortical folding

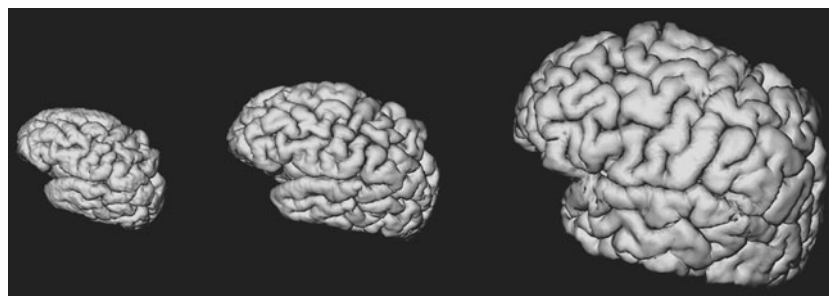
The quantitative and qualitative mapping of individual sulci appearance, mainly using the interface between the developing cortex and white matter zone, allows the coherent 3-D reconstruction of white matter surface. The reconstruction of white matter surface thus enables the in vivo measurement of cortical folding (Fig. 2). A sulcation index can be derived and allows measurement of variations with age, gender and presence of brain lesions and highlights early inter-hemispherical structural asymmetries that may be related to the cortical functional specialisation of the brain.

**Fig. 1** **a** Longitudinal coronal T1-weighted MRI images of one child at 33 PCW, 40 PCW and 6 years of age. Note the inversion of the T1-weighted MRI signal intensity as well as the age-specific MRI properties of the cerebral (cortical and white matter) tissue. Development of the age-specific MRI segmentation techniques are based on these primary image contrasts of the cerebral anatomical structures. **b** Longitudinal fractional anisotropy (FA) maps in children ages 28, 36 PCW and 6 years. Red arrows indicate the high anisotropy in the frontal cortex at 28 PCW with the gradual decrease reaching the low values at 36 PCW and 6 years of life



Females have lower cortical surface and smaller volumes of cortex and white matter than males, but equivalent sulcation. During development the highest sulcal index is found in the central region, followed by the temporo-parieto-occipital region, with the lowest sulcation index in the frontal region, which confirms that the medial surface folds before the lateral surface, and that the morphological differentiation of sulci begins in the central region, and progresses in an occipitofrontal direction. Recent applications of similar image analysis tools to MR images from the fetal brain confirm the timescale of appearance of sulci and gyri to be similar to the results from postnatal preterm infants brain folding [34–36]. Specific early brain asymmetries have been described with the right hemisphere presenting gyral complexity earlier than the left. It is particularly evident at the level of the superior temporal sulcus (STS), which parallels

early functional competence in response to auditory stimuli in newborns. Asymmetries were further highlighted in three specific regions over the external cortical surface [3] with deeper STS on the right side, and a larger posterior region of the sylvian fissure on the left side, close to the planum temporal as well as larger anterior region of the sylvian fissure on the left side, close to Broca's region, both regions of later language function. The high complexity observed in the adult brain is present in the term newborn; more specifically, sulcal patterns become variable across individuals. Central sulci showed less interindividual variations than parietal, temporal and frontal sulci. These data have contributed to a new extended framework for modeling cortical folding presented recently [37]. It is based on a system of reaction-diffusion equations defined on a surface that evolves through the action of morphogens; this model



**Fig. 2** Computation of the hemispheric gray matter surface (40,971 vertices) in the longitudinally scanned subject at age 33 PCW, 40 PCW and 6 years. The cortex and the white matter were segmented using the newly developed fully automated neonatal segmentation [23] and were corrected manually. Computation of the gray surface was performed

using the MNI toolbox developed at ACE lab (<http://www.bic.mni.mcgill.ca/~alan/>). Computation of the white and gray matter surface allows the longitudinal measurements of the gyrification index, surface area and cortical thickness as well as the extensive study of appearance and development of primary, secondary and tertiary convolutions

allows introduction of noise (just like in biology of situations such as intrauterine growth restriction or brain lesions) that will lead to morphological variability in the brain sulcal pattern [1, 2].

Preterm birth dramatically changes the expected environment during development, and studies have shown that both cortical volume [38] and surface area [39] of extremely preterm infants imaged at term equivalent age were decreased and were less complex than in normal infants, and this impairment seemed to increase with decreasing gestational age at birth [40].

That these early changes persist into childhood and potentially adulthood has been shown. Kesler noted abnormalities in sulcation in the temporal lobes of prematurely born children when compared to term control subjects at school age [41]. Twins and newborns born after poor intrauterine growth (IUGR) were found to have reduced brain surfaces and reduced sulcation indexes. These differences were paralleled with poorer neurobehavioral performance [1]. Comparison of monozygotic and dizygotic twins has further shown that degree of gyral and sulcal concordance was not different between the two, which indicates an important environmental component in early cortical folding [42]. During adolescence, when mature cortical folding is established, changes in cortical thickness are indicators of functional development [28]. Regionally specific trajectories of cortical thinning correlate with lower, normal or higher IQ [31], and pathologies such as attention deficit hyperactivity disorder are associated with delayed cortical thinning [5].

Then again, infants with early white matter lesions (WMI) showed a trend to increased gyrification in overlying cortex [2, 43] but reduced gray matter volume.

In fetuses with the well-known diagnosis of ventriculomegaly, usually diagnosed by antenatal ultrasound, high-resolution MRI was able to assess both brain tissue volumes and gyrification and found no difference in absolute brain tissue volumes but reduced cortical folding in parieto-occipital cortex overlying the area of predominant ventricular dilatation. The authors conclude that while tissue volumes seem to be preserved, cortical folding may be affected in regions where ventricles are dilated [44]. The genetic control of cortical convolutions [45] and its tight relationship with the cortical fiber ingrowth [46] suggest that the variability in appearance of gyri and sulci depends on the normal ingrowth of fibers. As the subplate zone, a “fiber waiting compartment” exists in the fetal and early postnatal period (the appearance of the stable primary gyri and sulci coincides with the thalamocortical ingrowth) the variable secondary and tertiary gyri and sulci appear parallel with the disappearance of subplate zone and ingrowth of long and short corticocortical association fibers [13, 18].

## Connectivity by DTI

Studying white matter development with in vivo imaging was largely impossible prior to the use of advanced magnetic resonance techniques, diffusion imaging being of particular interest in the assessment of the white matter microstructure during development [9]. The distance that a molecule diffuses in one direction in space may or may not be the same as in some other direction; thus, we measure these differences by measuring the diffusion anisotropy. Diffusion MRI measures the micron-scale displacement of water molecules. As evidenced in many experimental studies, axonal membranes play the primary role for anisotropic diffusion in the white brain matter. Eigenvector maps and RGB color-coded maps indicate the orientation of the major eigenvector providing an indication of the direction in which water diffusion is highest (typically parallel to white matter fiber fascicles). The first eigenvalue often referred to as axial diffusivity was shown to be affected by axonal integrity [47]. The second and third eigenvectors describe diffusivity perpendicular to the axial diffusivity. Radial diffusivity represents the average of the second and third eigenvectors; it was shown to be affected by changes in axon caliber and myelin ensheathment [48].

Tractography algorithms follow these discrete orientation estimates from point to point to reconstruct the white matter pathways and thus the global connectivity of the brain. The use of diffusion tensor imaging (DTI) has allowed visualization of early white matter connectivity demonstrating the existence of interhemispheric callosal fibers in the non-myelinated stage at 28 weeks of gestation and has, for the first time, further allowed characterization of differences in white matter connectivity in preterm vs. full-term infants [9] and the effects of injury to the white matter in prematurity [10]. Since those early studies, DTI has seen many methodological developments, which have allowed improved resolution and whole-brain coverage in reasonable scanning time, as well as becoming multidirectional to begin to address complex brain white matter structure.

In order to perform DTI, the  $b$  value at which to make the measurement has to be optimized, as it differs between the newborn and adult brain. In general, a  $b$  value corresponding to approximately  $1.1/D_{av}$  provides the best signal-to-noise ratio for such a measurement [49]. Typical DTI acquisition sequences for the newborn brain are given in Table 1 (reproduced from Hüppi [50]). Nevertheless, the sensitivity of DTI images to motion during acquisition appears to be a crucial problem with unsedated newborns [51]. For fetal brain imaging, DWI and DTI sequences have been adapted to be performed within a breath-hold of the mother. These sequences rely on fast spin-echo with echo-planar readouts with short TR (2,500 ms,  $b=600$  s/mm<sup>2</sup>) [52].



**Table 1** EPI DTI sequence parameters for newborn reproduced from [50]

	1.5 T	3 T
<i>b</i> -value 1	0 s/mm <sup>2</sup>	0 s/mm <sup>2</sup>
<i>b</i> -value 2	700 s/mm <sup>2</sup>	700 s/mm <sup>2</sup>
Diffusion gradients	30–60	30
EPI factor	128	128
Slice thickness	2.0 mm	2.0 mm
TR	6,100 ms	8,100 ms
TE	90 ms	86 ms
FoV	192 mm	192 mm
Base resolution	128	128
Time	4.40 min	4 min

*EPI* echo-planar imaging, *DTI* diffusion tensor imaging, *TR* time to repeat, *TE* echo time, *FoV* field of view

In ex vivo DTI studies on fetal brain development, high angular resolution diffusion imaging (HARDI) has been recently proposed [53].

The four main approaches to analyzing DTI data are region of interest (ROI) quantification, voxel-based morphometry, histogram analyses and tract-based analysis. Manual ROI selection and quantification is the most frequently used. This method is time consuming and is characterised by a large inter-rater variability due to a bias in ROI selections. Nevertheless, it has been a gold standard and a first step in connectivity and network maturation analysis. For example, early fetal ROI-driven tractography reveals the timetable of appearance of first fiber bundles and thus is able to show, for example, early maturation of the limbic system [15, 18]. Voxel-based morphometry (VBM) is an alternative method initially designed to quantify regional changes in volume on conventional imaging [54]. Its automated analysis eliminates a priori knowledge and user bias but it is vulnerable to error due to registration and normalization. Tract-based spatial statistics, or TBSS, is an alternative method [55]. It is based on the realignment of the fractional anisotropy maps of all subjects onto a fractional anisotropy map skeleton. All results from methods based on spatial registration need to be attentively evaluated when used in the presence of large focal lesions or areas of crossing fibers, where voxel-wise comparisons can lead to erroneous results.

Connectomics [56, 57] has been recently developed and used to report altered connectivity due to disease in adolescent and adult subjects. In recent years, several studies have proven the ability of connectomics to exhaustively map inter-regional connectivity within the brain, building a structural connectivity matrix (or connectomes), to identify regions with altered connectivity (Fig. 3).

Results throughout brain development have shown the core regions have higher anisotropy than the peripheral regions for all white matter tracts. Projection

fibers together with the corpus callosum are the most prominent fibers identified in the newborn; limbic fibers are present whereas association fibers, such as the superior longitudinal fasciculus, are difficult to be delineated with the current resolution in in vivo newborn imaging.

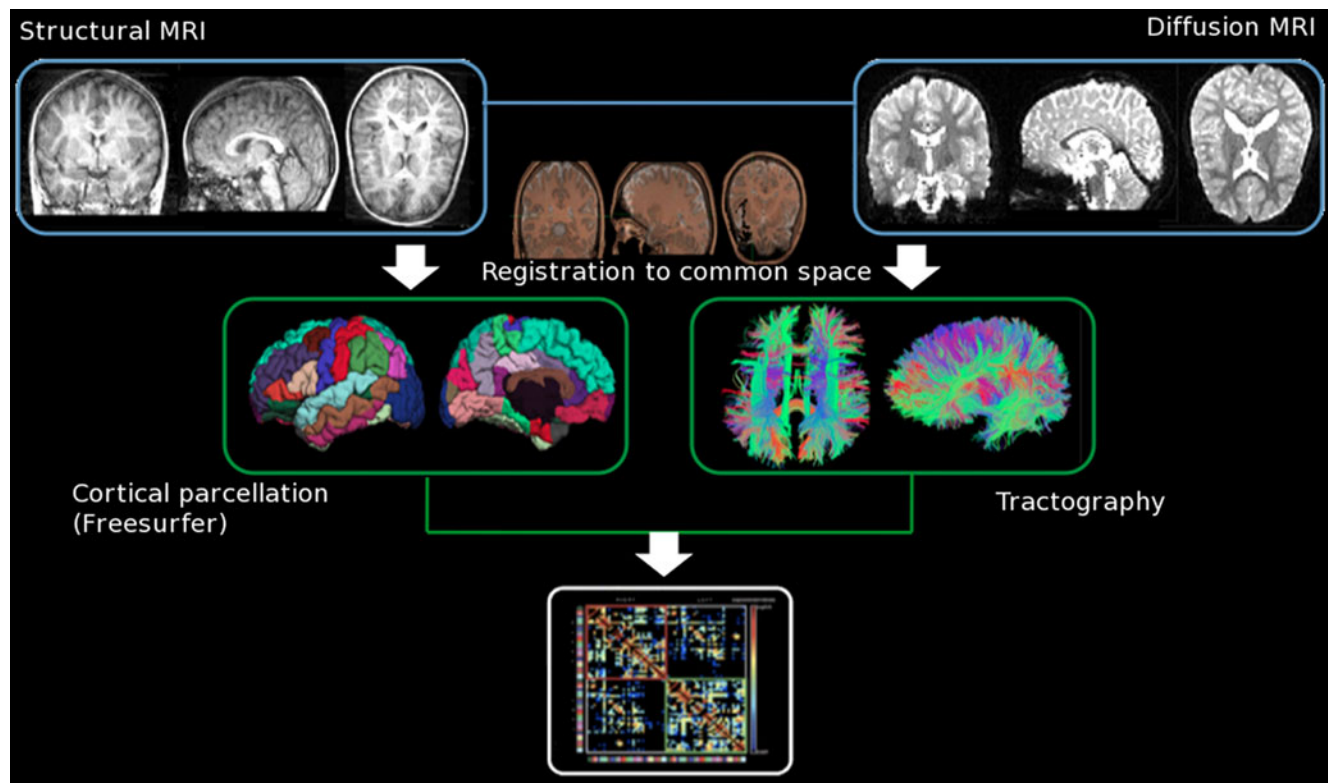
In order to understand the underlying structural changes for the rapid development of motor and cognitive functions in the early months of postnatal life, Dubois et al. [7] defined relative maturation phases of different white matter fiber tracts. Corticospinal tracts appear as the most mature bundle in the first 4 months of life and the anterior limb of the internal capsule and the cingulum as a limbic structure as the least mature bundles. Furthermore, this study allowed the differentiation of maturational stages within a functional system, for example, with the fornix in the limbic system being in an advanced maturational phase compared to the cingulum, and the fornix being involved in associative learning, which is important in early functional development.

Tract specific changes occur rapidly during the first 3–6 months and slower thereafter with stability after 24 months. From 6 years to 17 years, FA increases only slowly and mean diffusivity decreases somewhat in most studied association and projection tracts [58] (Fig. 4).

Tract-based spatial statistics analysis (TBSS) combined with probabilistic tractography is a newer method of defining changes in microstructure of the developing brain [59, 60, 55]. Many perinatal conditions, such as prematurity, perinatal asphyxia or chronic lung disease, have been shown to lead to alteration of microstructural brain development assessed by TBSS, and results have identified lower FA as a structural biomarker for later neurodevelopmental deficits [61–63]. Microstructural long-term brain changes as a result of prematurity have been reviewed in detail by Ment et al. [64].

Developmental changes in FA during adolescence were mainly due to changes in axial diffusivity and more pronounced between early adolescence and adulthood than between late childhood and adolescence [65]. Factors that might influence the changes in axial diffusivity at this age are increased neurotubules, neurofilaments and glial cells and increased fiber coherence as pruning comes to its end [66]. These long-term changes fit with the assumption that learning and experience are accompanied by structural changes. Experience-related changes in diffusion characteristics have been shown in piano players practicing [67] after short intensive video game tasks [68] and provide evidence in support of the experience-based structural plasticity in the brain.

It is well accepted that DTI, in its current form, cannot characterize small fiber systems; thus, one issue that should be established is the extent to which the reconstructed fiber



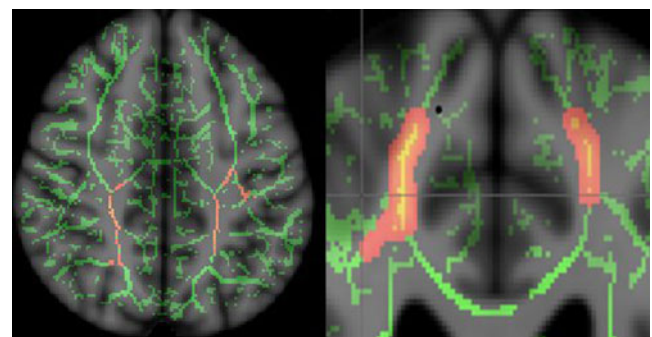
**Fig. 3** Generation of a brain connectome: In order to study neuronal connections as a whole, the method generates a connectivity matrix measuring the strength of connectivity (DTI-FA based) of all connections in the brain between a preset number of cortical regions defined on conventional MRI. Each matrix is symmetrical and subdivided in four quadrants, each of them representing the connections between hemispheres. The *top left quadrant* represents the intrahemispherical

connections of the right hemisphere (right-right connections). The *top right quadrant* shows the density of fibers' connectivity between the right hemisphere and the left one, thus the interhemispherical connections that are also shown in the *bottom left quadrant*. In the *bottom right and last quadrant*, the intrahemispherical connections in the left hemisphere are represented

systems reflect brain connectivity. New methodologies that extract compartment specific, micro-structural information from diffusion imaging are being evaluated. CHARMED [69, 70] and AxCaliber [71] are such new diffusion imaging schemes that provide unique abilities to assess axonal diameter [72] in vivo and provide an extremely powerful tool to investigate the underlying mechanism of myelination and axonal diameter changes occurring during development. A better understanding of these developmental cellular structural modifications can then directly be used to improve human diffusion signal modeling.

Another MRI approach has recently been proposed to exploit subtle magnetic susceptibility differences between brain tissues to improve anatomical contrast and resolution. These susceptibility differences lead to resonance frequency shifts that can be visualized by reconstructing the signal phase in conventional gradient echo acquisition techniques [73]. With a contrast based on the magnetic susceptibility differences between tissue type and tissue junctions, phase imaging offers a new and unique type of contrast. Phase contrast has been shown to be influenced by deoxyhemoglobin, vascularity, iron, myelin, geometry and orientation of tissue, as well as

microstructure, chemical exchange and presence of macromolecules such as in ECM [74]. We have recently explored these new contrasts in the rodent developing brain [75]. A recent first study on phase imaging in the newborn actually hypothesizes



**Fig. 4** Typical example of a tract-based spatial statistics (TBSS) analysis, where two groups of DTI (FA maps) images are compared. Mean fractional anisotropy (FA) skeleton overlaid on the mean FA map for comparison of the two groups. Regions of the mean FA skeleton in green represent areas where there were no significant differences in FA values between the two groups whereas areas in red are regions where the FA is significantly different in one group

that phase difference between the neonatal and adult brains may be due to a different macromolecule concentration in the unmyelinated brain of the neonates and thus a different frequency due to water macromolecule exchange [76].

The human brain is organized into a collection of interacting networks with specialized functions to support various cognitive functions and therefore one can argue that these networks are structurally present in some form.

Recent research has suggested that the brain manifests small-world topology, which implicates both global and local efficiency at minimal wiring costs, and also modular organization, which indicates functional segregation and specialization. Taking a graph theoretic approach, Yap et al. [77] attempt to shed light on this matter by an in vivo study, using DTI-based fiber tractography on children with longitudinal data collected at average ages of 2 weeks, 1 year, and 2 years. Their results indicate that the small-world architecture exists at birth with efficiency that increases in later stages of development. The brain network seems to evolve progressively from a local, predominantly proximity-based, connectivity pattern to a more distributed, predominantly functional based, connectivity pattern. These observations suggest that the brain in the early years of life has relatively efficient systems that may solve similar information processing problems, but in divergent ways. Adverse antenatal conditions might alter these networks and change connectivity efficiency as measured by graph theory [78].

### Functional connectivity (resting state fMRI)

Functional MRI connectivity (fcMRI) assesses baseline neural processing [79–82] using the spontaneous Blood Oxygen Level-Dependent (BOLD) signal intensity time course's coherent oscillations within a neuronal network. Smyser et al. [81] identified multiple networks, their regional growth and their connections with homotopic counterparts during development. They showed the presence of resting state networks in the primary visual cortex, bilateral sensorimotor areas, bilateral auditory cortex, a network including the precuneus area, lateral parietal cortex, and the cerebellum as well as an anterior network that incorporated the medial and dorsolateral prefrontal cortex [81]. Similar to earlier structural DTI assessments, the presence of interhemispheric functional connectivity was established as early as 26 weeks of gestation. The comparison of prematurely born infants with newborn infants born at term revealed a reduction of long-range network connectivity. A recent fcMRI study on a large cohort of 2-week-old to 2-year-old infants revealed regional developments of brain wiring efficiency and the evolution of functional hubs, which suggests a differential developmental trend for primary and higher-order cognitive functions during the first two years of life [83].

### Future

Even though high-resolution imaging has enabled researchers to study brain architecture during development in an unprecedented way, the mechanisms by which the brain establishes its complex structural and functional networks are only starting to be understood. Wedeen et al. [84] recently described the geometric structure of brain fiber pathways in several species including humans that indicate that the fiber pathways are organized according to a grid, and Clouchoux et al. [85] derived a spherical coordinate system from the pattern of human cortical folding. Furthermore, Chen et al. [86] recently studied human brains by surface reconstruction, atlas mapping and added genetic analysis. By doing this, the cortex could be parcellated in 12 regions according to genetic information. This new approach allowed comparison of genetic topography with cytoarchitecture and striking similarities could be defined [87].

Combining these methods in the future and modeling the hierarchical organization of the brain might ultimately help to understand the mechanisms underlying complex brain structure function relationships.

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